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10/019,797	07/26/2002	Achim Gopferich	MB9962P	1932

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EXAMINER	
WESTERBERG, NISSA M	
ART UNIT	PAPER NUMBER
1618	
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/019,797	GOPFERICH ET AL.	
	Examiner	Art Unit	
	Nissa M. Westerberg	1618	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *20 July 2010*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-3,5,9-32,36-38,41-44,63 and 65-74* is/are pending in the application.

4a) Of the above claim(s) *11,16-32,63,65 and 66* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-3,5,9,10,12-15,36-38,41-44 and 67-74* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Continued Examination Under 37 CFR 1.114

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on June 21, 2010 has been entered.

2. Applicants' arguments, filed June 21, 2010 and July 20, 2010, have been fully considered but they are not deemed to be fully persuasive. The following rejections and/or objections constitute the complete set presently being applied to the instant application.

Comments and Notes

3. One of the amendments made to claim 1 in the most recent set of amendments states that the second functional end group c2) is not a hydroxyl group or carboxylic acid but the claim also states that c2) is an amine. Based on this positive recitation, the

negative limitation is redundant. It is respectfully suggested that the negative limitations for the second functional end group be deleted from the claim.

Response to Amendment

4. The declaration under 37 CFR 1.132 filed June 21, 2010 is insufficient to overcome the rejection of claims based upon Domb further in view of Greenwald as set forth in the last Office action because: regardless of whether the PLA-PEG polymers disclosed in the each of the Domb and Hirosue references are the same, these references were applied independently of each other. The declaration was sufficient in regards to the Hirosue reference. The relevant question is whether the polymers disclosed in each reference in combination with Greenwald read on the instant claims. Both ester and ether linked PLA-PEG read on the c1) terminal end group that becomes a portion of polymer backbone in the final polymer. That Domb does not teach amine terminated PEG is the deficiency that is remedied by the secondary reference of Greenwald. All of the facts and opinions set forth in the declaration relate solely to the primary references and do not touch upon the teachings of the Greenwald reference. Beyond a statement at paragraph 30 of the declaration that Domb and Hirosue in the combinations set out by the Examiner do not disclose or suggest a free primary amino terminated PEG-PLA compositions, Dr. Vasudevan does not provide his reasoning as to why the person of ordinary skill in the art would not modify the PEG-PLA polymers of Domb with the teachings of Greenwald as the NH2-PEG that allow for conjugation to a

chemotherapy drug. Such conclusory statements without an indication of how that conclusion was arrived at are not persuasive.

Specification

5. The amendment filed October 28, 2002 is objected to under 35 U.S.C. 132(a) because it introduces new matter into the disclosure. 35 U.S.C. 132(a) states that no amendment shall introduce new matter into the disclosure of the invention. The added material which is not supported by the original disclosure is as follows:

- Page 9, lines 11 – 21 which describe the contents of EP 0844269 and WO 95/03356, documents which were not referenced in the PCT application so their contents could not have been incorporated by reference. The instant application is the National Stage Entry of that application. No new matter can be introduced when a PCT enters the national stage.
- Page 12, lines 8 – 13 which reference the generation of substrate pattern with the reactive group c) being selected from 1) an at least bifunctional molecule with at least one free functional group and/or 2) a functional group, and block copolymers obtained with this. No certified translation of the PCT application, published in German, has been filed to determine if such limitations were present elsewhere in the specification to provide support for this limitation.
- Page 22, lines 19 – 21 which adds a proviso that an at least bifunctional molecule is used as reactive group c) for a block copolymer according to one of

claim 1 – 19. Based on the originally filed English claims in the national stage application, claim 1 required that if the hydrophilic polymer b) is polyethylene glycol, the reactive group c) is not hydroxyl. Due to the amendments to the claims which now require PEG as the hydrophobic polymer and the presence of a reactive group c) of a hydroxyl, this statement adds new matter to the specification.

Applicant is required to cancel the new matter in the reply to this Office Action.

If Applicant is in disagreement with the Examiner regarding support for the amendments, Applicant is respectfully requested to point to page and line number wherein support may be found for the instant invention. If reference is made to the German application, a certified English translation of that document should also be provided.

Claim Objections

6. Claim 3 is objected to under 37 CFR 1.75(c), as being of improper dependent form for failing to further limit the subject matter of a previous claim. Applicant is required to cancel the claim(s), or amend the claim(s) to place the claim(s) in proper dependent form, or rewrite the claim(s) in independent form. A primary amine group as one of the terminal end groups has already been required by claim 1.

7. Claim 5 is objected to under 37 CFR 1.75(c), as being of improper dependent form for failing to further limit the subject matter of a previous claim. Applicant is required to cancel the claim(s), or amend the claim(s) to place the claim(s) in proper dependent form, or rewrite the claim(s) in independent form. Claim 1 requires the hydrophilic polymer b) comprise polyethylene glycol (PEG) and the Markush group in claim 5 recites many polymers that do not contain PEG.

Claim Rejections - 35 USC § 112 – 1st Paragraph

8. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

9. Claims 1 – 3, 5, 9, 10, 12 – 15, 36 – 38 and 41 – 44 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This is a new matter rejection.

The polymers of amended claim 1 comprise the diblock structure c2)-b)-c1)-a) (line 3 of claim 1) and the element b) is defined (lines 7 – 8) as polyethylene glycol (PEG) and a reactive group comprising c1) and c2). With this definition of b), the actual structure of the diblock polymer being claimed is c2)-[PEG with c1) and c2) functional

end groups]-c1)-a). The Examiner was unable to locate support in the specification as filed for polymers with this structure.

Claim 1 also requires that the second functional end group is "capable of efficiently and expeditiously covalently binding surface-modifying substance d)" (lines 19 – 20). The specification discloses that the preferential orientation of the hydrophilic polymer b) towards the surface when placed in aqueous media allows for “free accessibility of surface-modifying substance d) to the reactive group c) for binding” (p 10, ln 2 – 3 of June 10, 2004 copy of specification). “Free accessibility” is insufficient to support a claim limitation of "efficient and expeditious” covalent binding of the c2) functional end group with surface-modifying substance d).

Amended claim 1 also requires that binding of surface-modifying substance d) to the copolymer-linked bifunctional reagent occurs “without substantial loss of bioactivity of such substance in an instant reaction, without further reaction or activation steps and not exceeding a reaction time of about two hours at room temperature following dipping or incubation of the shaped body or particles into a mainly aqueous solution or suspension containing the unmodified and native surface-modifying substance d)." The Examiner was unable to find support for the binding of the surface-modifying substance d) occurring without substantial loss of bioactivity. The Examiner was also unable to locate support for the absence of further reaction or activation steps. While a two hour reaction time was disclosed on p 29, line 12 of the specification, no indication of the temperature is given. The use of such an incubation time in one example is insufficient to support the general claim limitation of the reaction time not exceeding 2 hours

regardless of polymer and surface-modifying substance d) now recited in claim 1. No indication of unmodified and native surface-modifying substance d) was found in original specification.

The rest of the claims fall therewith.

If Applicant is in disagreement with the Examiner regarding support for the amended claim, Applicant is respectfully requested to point to the paragraph number or page and line number wherein support may be found for the instant invention.

10. Claim 33 is rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This is a new matter rejection.

The claim requires that the hydrophobic polymer a) have a molar mass greater than 1,000 Da. P 16, ln 25 – 28 of the clean copy of the specification indicates that the hydrophobic polymer is particularly preferred to be "polylactide, e.g., a poly(D,L-lactide), preferably with a molar mass in a range from 1,000 to 100,000, in particular up to 50,000 Da." This does not provide support for a molecular weight limitation relating to all the hydrophobic polymers recited in claim 1 and for polylactides with molecular weights of greater than 100,000 Da.

If Applicant is in disagreement with the Examiner regarding support for the amended claim, Applicant is respectfully requested to point to the paragraph number or page and line number wherein support may be found for the instant invention.

11. Claim 70 is rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This is a new matter rejection.

This claim contains the limitation that the "hydrophilic block contains from a single ethanolamine to a poly(ethanolamine)". P 16, ln 13 discloses a substituted PEG such as PEG-NH_2, which would contain a single ethanolamine (-O-CH_2CH_2-NH_2). This disclosure is insufficient to support the present of more than one ethanolamine up to a poly(ethanolamine) as recited by claim 70.

This claim also contains the limitation that the polymer has a molecular weight of 100-100,000 Da. P 16, ln 25 – 28 of the clean copy of the specification indicates that the hydrophobic polymer is particularly preferred to be "polylactide, e.g., a poly(D,L-lactide), preferably with a molar mass in a range from 1,000 to 100,000, in particular up to 50,000 Da." The cited section only provides support for molecular weight ranges of 1,000 – 100,000 Da and 1,000 – 50,000 Da.

If Applicant is in disagreement with the Examiner regarding support for the amended claim, Applicant is respectfully requested to point to the paragraph number or page and line number wherein support may be found for the instant invention.

12. Claim 73 is rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This is a new matter rejection.

Claim 73 requires a polymer with two different repeating units with at least about 19 of one repeating unit and at least about 5 of the other repeating unit. The Examiner was unable to locate any discussion as to particular number of repeating units present in a particular polymer. While specification and examples may provide support for the general structure of the polymer, the Examiner was unable to locate support for the number of lactide and ethylene glycol units which are present in the final polymer prepared in the examples.

If Applicant is in disagreement with the Examiner regarding support for the amended claim, Applicant is respectfully requested to point to the paragraph number or page and line number wherein support may be found for the instant invention.

13. Claim 74 is rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which

was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This is a new matter rejection.

Claim 74 requires the polylactide moiety have a maximum molar mass of about 100,000 Da. The specification as originally filed (p 16, ln 25 – 28 of the clean copy of the specification) indicates that the hydrophobic polymer is particularly preferred to be "polylactide, e.g., a poly(D,L-lactide), preferably with a molar mass in a range from 1,000 to 100,000, in particular up to 50,000 Da." The cited section provides support for polylactic moieties having molecular weight ranges of 1,000 – 100,000 Da and 1,000 – 50,000 Da, but not "a maximum molar mass of about 100,000 Da". The current claim limitation also encompasses polylactic acid moieties with a molecular weight of less than 1,000 Da but such values were not disclosed in the application as originally filed.

Claim 74 also requires the PEG moiety to have a maximum molar mass of about 10,000 Da. The specification as originally filed (p 16, ln 17 – 18) recites molar mass for the PEG as being between 200 and 10,000 Da, with 1,000 – 10,000 Da being particularly preferred. This does not provide support for "a maximum molar mass of about 10,000 Da" as the current claim limitation also encompasses PEG moieties with a molecular weight of less than 200 Da but such values were not disclosed in the application as originally filed.

If Applicant is in disagreement with the Examiner regarding support for the amended claim, Applicant is respectfully requested to point to the paragraph number or page and line number wherein support may be found for the instant invention.

Claim Rejections - 35 USC § 112 – 2nd Paragraph

14. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

15. Claims 1 – 3, 5, 9, 10, 12 – 15, 36 – 38 and 41 – 44 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. In line 8 of claim 1, a reactive group comprising c1) and c2) is required as part of block b) of the diblock polymer. Later in the claim, c1) and c2) are defined to be a first and second functional end group and c1) must be bound directly to polymer b). However, with the block b) comprising reactive group comprising c1), c2) and PEG, it is unclear how the second c1) can meet the structural limitations of being directly bound to b) while also meeting the limitation. of the overall polymer having the structure c2)-[block PEG comprising reactive end groups c1) and c2)]-c1)-a) It is unclear how either c1) can be a functional end group as both c1)'s are contained within the polymer and not at the end. It is also unclear if the primary amino group of c2) is part of the bifunctional molecule referenced in line 14 of claim 1; if the primary amino group, bifunctional molecule and surface-modifying substance all three distinct entities or if a bifunctional surface-modifying substance reacting with the primary amino group would meet the limitation of claim 12, for example in which both the surface modifying substance d) and a

bifunctional molecule are required to be present, as long as the second functional group is not the same as c1). Please clarify.

16. Claim 67 rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Claim 67 recites the limitation "the reactive group" in line 5. There is insufficient antecedent basis for this limitation in the claim.

Claim Rejections - 35 USC § 103

17. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

18. The factual inquiries set forth in *Graham* v. *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

19. This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of

the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

20. Claims 1, 5, 9, 10, 12 – 15, 36 – 38, 41 – 44 and 67 – 74 were rejected under 35 U.S.C. 103(a) as being unpatentable over Domb et al. (US 6,365,173) in view of Greenwald et al. (Bioorg Med Chem, 1998). This rejection is MAINTAINED for the reasons of record and those set forth below.

Domb et al. teaches block copolymers of PLA (polylactic acid) with poly(ethylene oxide) such as $[(\text{D- or L-lactic acid})_x\text{-co-ethylene oxide})_y]_z$ wherein x, y= 10 to 5,000 and z= 0 to 100 (col 6, ln 24 – 26, 30 – 31). When z = 1, a diblock polymer is prepared. Higher values of z lead to polymers which comprise a polyethylene glycol-lactic acid diblock repeating unit. Pre-prepared polymer blocks with hydroxyl and carboxylic acids can be conjugated via a number of linkages (col 4, ln 40 – 47). In example 11, an AB block copolymer of L-PLA-b-PEG is prepared. These stereoselective polymers are complexed with a bioactive molecule that can be bound to the complex by ionic, hydrogen or other non-covalent binding reactions (col 2, ln 47 – 53). Covalent bonds can also be used to link the bioactive molecule to the stereocomplexes (the polymeric portion; col 7, ln 1 – 5). Peptides, proteins, nucleotides, sugars, carbohydrates and

other synthetic or natural drugs can be used as the bioactive molecule (col 2, ln 56 – 60; col 6, ln 52 – 67). Standard polymeric processing techniques are used to form particles, rods, tablets, films or beads, which read on the implantable, pre-shaped body or particle of the instant claims.

Domb et al. does not disclose a primary amine end group on the PEG.

Greenwald et al. discloses conjugation of NH2-PEG to camptothecin (Scheme 1, p 554). Conjugation of polymers to cytotoxic drugs can be used for drug delivery by increasing solubility, enhancing tumor accumulation and increasing circulatory retention (p 551, col 1, ¶ 1). Because camptothecin does not contain a carboxylic acid group that would react with an amine group to couple the drug to the NH2-PEG, A small heterobifunctional linker is added at the 20-OH group with a carboxylic acid group was added to the compound. (p 553, col2, ¶ 1).

It would have been obvious to the person of ordinary skill in the art at the time the invention was made to use a NH2-PEG as one of the blocks in the PLA-PEG block polymers of Domb. The person of ordinary skill in the art would have been motivated to make those modifications to prepare a polymer for conjugation with bioactive molecules with a different functional group to use for drug coupling and reasonably would have expected success because Greenwald et al. uses NH2-PEG for coupling the polymer to a drug containing a carboxylic acid. While the camptothecin of Greenwald does not contain a group capable of coupling to NH2-PEG in its unmodified and native state, Domb et al. teaches a wide variety of bioactive molecules that can be coupled to polymers for drug delivery. Peptides and proteins contain carboxylic acids group in their

native and unmodified state that would react with the primary amine of NH2-PEG-PLA to form drug-polymer conjugates utilizing such peptides or proteins.

The orientation of polymer is determined by the block structure of the polymer and as polymers with the same block structure are taught by Domb et al. as are recited by the instant claims, the same orientation must result when these polymers are used in shaped bodies. Varying sizes of polymer (brought about by varying the value of x and y) are taught by Domb and will determine the size of the hydrophobic and hydrophilic blocks of the polymers that will determine the exact behavior of objects made from such polymers. Thus, the molecular weight of the polymer blocks is clearly a result effective parameter that a person of ordinary skill in the art would routinely optimize. Optimization of parameters is a routine practice that would be obvious for a person of ordinary skill in the art to employ and reasonably would expect success. It would have been customary for an artisan of ordinary skill to determine the optimal number of repeating units in each polymer block to produce a polymer with the desired properties for a particular drug delivery system or application.

The claim also requires that the block structure of the polymer permits binding of the surface modifying substance d) under certain conditions. The combination of Domb and Greenwald teach a coupling reaction between NH2-PEG with carboxylic acid group. The reaction time will be optimized depending on the reactivity of the materials being used and the extent of reaction required. For example, incomplete binding of the bioactive agent to all potential sites may not be desirable as that would result in too high

drug loadings that would provide too much drug and/or decrease the bioactivity of the bioactive molecule attached to the surface.

Applicants traverse this rejection on the grounds that the polymeric structure from p 3 of the final office is incorrect and such polymers cannot be synthesized. The use of \Ho-PEG-OH will result in triblock polymers. The polymer of example 11 can only be synthesized using with a terminal methoxy group which is not reactive and cannot be converted to a reactive group with destroying the polymer.

These arguments are unpersuasive. The instant claims use comprising language and even if triblock polymers were prepared, such polymers are not excluded from the claims. The polymers comprise a diblock with the required structure and additional polymeric blocks can be present in the polymer. Domb disclose that the PLA blocks were synthesized and then conjugated to blocks of polyhydroxybutyrate or PEG, for example (col 5, ln 37 - 48).

Applicant also argues that most of the reactions of Greenwald cannot be conducted with PLA as it would dissolve under the chosen (e.g., currently claimed) conditions, thus further diverging from the claim limitations and the surface-modifying substance conditions.

These arguments are unpersuasive. It is not clear to the Examiner what the currently claimed conditions that would cause dissolution are and how those limitations impact the patentability of the copolymer and articles made from that polymer. The instant claims are drawn to products so such limitations would make the claims product-

by-process. As the structure of the final polymers is the same, the burden is shifted to Applicant to demonstrate that the product produced by the process of the prior art is not the same and is not obvious when compared to the product produced by the claimed process (see MPEP 2113). Greeenwald demonstrate conjugation of a drug containing a carboxylic acid with the primary amino of amino-PEG. If conditions for that coupling would result in the disruption of the PEG-PLA, the drug could be conjugated to the PEG and then the drug-PEG conjugate could be linked with PLA block to form the final polymer. Domb disclose a wide variety of bioactive molecules for conjugation to the polymers, and the selection of linkage moieties between the polymer and drug and the order of assembly for the various pieces of the final molecule is within the skill of the artisan having ordinary skill in the art. While the camptothecin conjugated in Greenwald does not contain a carboxylic group, which was synthetically added, bioactive molecules that can be conjugated include peptides, which contains a carboxylic acid group without further reaction or activation steps in the unmodified and native state that would react with the primary amino group on the PEG.

Applicants argue that the disclosure of the first reference as a whole does not reveal all of the limitations of any of the currently pending independent claims which shortcomings are not overcome by the disclosure of the second reference and *vice versa*.

These arguments are unpersuasive. Without being more specific about the limitations that the references fail to disclosure, the Examiner is unable to respond with any specificity beyond the above discussion of the teachings of the reference and other

arguments. While Domb does not disclose PEG with a terminal amine group, Greenwald cures that deficiency as discussed in greater detail above, allowing for conjugation of the PEG-PLA polymer to bioactive molecule that contain groups that react with the amine group to form the desired conjugate.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Nissa M. Westerberg whose telephone number is (571)270-3532. The examiner can normally be reached on M - F, 8:00 a.m. - 4 p.m. ET.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Michael G. Hartley can be reached on (571) 272-0616. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Michael G. Hartley/
Supervisory Patent Examiner, Art Unit 1618